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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/872,162	05/31/2001	Isaiah J. Fidler	UTSC:643US/SLH	8776

7590 10/21/2003

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	12

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/872,162	FIDLER ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover she t with the correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2003 and 05 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-194* is/are pending in the application.

4a) Of the above claim(s) *1-132,136 and 143-194* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *133-135 and 137-142* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-194 are pending in the present application.

Applicants' amendments filed on 6/2/03 and 8/5/03 in Paper Nos. 12 and 13, respectively have been entered.

This application contains claims 1-132, 136 and 143-194 drawn to an invention nonelected without traverse in Paper No. 10. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Accordingly, claims 133-135, 137-142 are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

With respect to the elected invention and species, claims 133-135 and 137-142 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(1) A method of inhibiting cancer growth in a host having a cancer, said method comprising:

a) isolating cancer cells from the host;

b) rendering said cancer cells inactive;

c) reintroducing said inactivated cancer cells into said host in a pharmaceutical composition, said pharmaceutical composition further comprising an insect cell and interferon-β;

does not reasonably provide enablement for a method of treating cancer in a host utilizing inactivated cancer cells and an insect cell composition without the presence of interferon-β. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same reasons already set forth in the previous Office Action in Paper No. 11 (pages 3-7).

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on June 02, 2003 in Paper No. 12 (pages 3-5) have been fully considered, but they are not found persuasive.

(1) With respect to phrase "inhibiting cancer" recited in the preamble of the claims, Applicants argue that anything that "inhibits" a cancer also "treats" a cancer, and that treatments do not require eradication of cancers.

Since none of the terms "inhibiting" or "treating" are clearly defined in the specification, Examiner interprets broadly a method of inhibiting cancer as claimed encompasses a broad range of therapeutic and/or prophylactic effects that include the inhibition of a tumor growth, eradication of a tumor as well as preventing the reoccurrence of a cancer in a host. As already noted in the previous Office Action, the

present disclosure fails to provide sufficient guidance for a skilled artisan on how to obtain such broad therapeutic and/or prophylactic effects contemplated by Applicants in the methods as claimed. For example, even with the utilization of lyophilized H5 insect cells infected with a recombinant baculovirus expressing IFNβ in combination with irradiated B16BL6 tumor cells, tumor growth is still observed upon challenge of the vaccinated mice with viable B16BL6 tumor cells, although the challenge tumor growth is statistically significantly reduced (see Fig. 23). Additionally, intratumoral injection of IFNβ alone or in combination with an insect cell composition does not eradicate the treated cancer because tumor growth is still observed (see Fig. 24).

(2) With respect to the issue on the insect cell composition, Applicants argue that Applicants do not understand why a mixture of insect cells + interferon-β would not be expected to work in a manner similar to an insect cell composition comprising interferon-β being expressed in the insect cells.

Applicants' argument has been considered but is moot in view of a broader scope of enablement given. It is noted that the insect cell composition must contain interferon-β (an elected species of immunomodulators), because interferon-β is essential and necessary for the regression of tumor growth. As already noted in the previous Office Action, there is no statistically significant reduction in challenge tumor growth for the mixture of irradiated B16BL6 and H5BV cells or H5 cells (control insect cells) in comparison with the challenge tumor growth in naïve mice or in mice pretreated with irradiated B16BL6 alone (see Fig. 23).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 135 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the same reasons already set forth in the previous Office Action in Paper No. 11 (page 7).

Claim 135 recites the limitation "said immunomodulator is IFNβ" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim. This is because in the method of claim 133 on which claim 135 is dependent, there is no recitation of any immunomodulator. The metes and bounds of the claim are not clearly determined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 133-135 and 137-142 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sobol et al. (U.S. 5,681,562) in view of Dong et al. (Cancer Research 59:872-879, 1999; IDS), Smith et al. (U.S. 6,224,882) and Smith et al. (4,745,051; IDS) for the same reasons already set forth in the previous Office Action in Paper NO. 11 (pages 9-12).

With respect to the elected invention and species, the claims are drawn to a method of inhibiting cancer comprising: (a) isolating cancer cells from a host; (b) rendering said cancer cells inactive; (c) reintroducing said inactivated cancer cells into said host in a pharmaceutical composition, said pharmaceutical composition further comprising an insect cell composition; the same method wherein said insect cell composition further comprising IFNβ or wherein said insect cell composition comprising an exogenous DNA encoding IFNβ.

With respect to the enabled scope and elected species, Sobol et al. teach a method for inhibiting the growth of tumor cells in a patient comprising the stimulation of that patient's immune response against the tumor cells by administering to said patient a composition comprising tumor antigens and cytokine expressing cells genetically modified to express a cytokine gene product, wherein said cytokine-expressing cells are not tumor cells (see Summary of the Invention, cols. 2-3; and the claims). Exemplified cytokine genes to be expressed in the method of Sobol et al. include the genes for IL-2,

gamma-interferon (c-INF) and other cytokines readily available in the art (col. 5, lines 48-50). Sorbol et al. teach that apart from IL-2, other cytokines such as IL-4, alpha interferon (α-INF) and gamma interferon (c-INF) have been used to stimulate immune responses to tumor cells (col. 1, lines 43-46). Sobol et al. further teach that when viable tumor cells are utilized in immunizations as a source of tumor antigens, the tumor cells can be inactivated so that they do not grow in the patient, and inactivation can be accomplished by several methods such as irradiation prior to immunization (col. 7, lines 29-36). Tumor cells bearing tumor-associated antigens are isolated from the patient (col. 6, lines 61-62). Additionally, Sobol et al. teach that autologous and non-autologous cells can be selected and processed to generate cytokine expressing cells (col. 5, lines 33-44).

Sobol et al. do not specifically teach a method of reintroducing inactivated cancer cells in a pharmaceutical composition further comprising an insect cell composition comprising IFNβ to stimulate a systemic active immune response in a patient in need thereof to inhibit the growth of said cancer cells.

However, at the effective filing date of the present application, Smith et al. (U.S. 6,224,882) already teach that insect cells from the Lepidopteran species or insect cells subjected to baculovirus infection or their fractions can be utilized as an adjuvant for immunogenic, immunological, antigenic or vaccine compositions (see abstract and Summary of the Invention). Smith et al. (U.S. 6,224,882) further teach that the insect cells can be infected with a recombinant baculovirus expressing an epitope of interest or antigen.

Smith et al. (U.S. 4,745,051) also already teach that insect cells subject to recombinant baculovirus infection are capable of expressing any selected desired gene products, including the human IFNβ gene product that can be synthesized and efficiently secreted from the host insect cells (see Summary of the invention).

Dong et al. teach that it has been known in the art that IFNs can be efficacious against many hematopoietic neoplasms and some vascular tumors (page 872, col. 2, second full paragraph). Dong et al. further teach that IFNβ can inhibit tumor growth and metastasis of human prostate cancer cells by suppression of tumor angiogenesis and activation of tumoricidal host effector cells (see abstract). Furthermore, Dong et al. teach that IFNβ has been shown to be more potent than IFN-α at least in inhibiting for the proliferation of human prostate cancer cells (page 872, col. 2, second full paragraph).

Accordingly, at the effective filing date of the present application it would have been obvious and within the level of skill for an ordinary skilled artisan to modify the method of Sobol et al. by utilizing insect cells infected with a recombinant baculovirus expressing IFNβ as a source of cytokine expressing cells, for the stimulation of a systemic active immune response in a patient in need thereof to inhibit the growth of cancer cells in light of the teachings of Smith et al. (U.S. 6,224,882), Smith et al. (4,745,051) and Dong et al.

One of ordinary skilled artisan would have been motivated to carry out the above modification because insects cells whether genetically modified with a recombinant baculovirus expressing IFN-β or not, can function as an adjuvant for the co-

administered inactivated tumor cells to further stimulate a systemic active immune response specific to said tumor cells in a patient. Additionally, since IFNβ has been shown to be efficacious against many hematopoietic neoplasms, some vascular tumors as well as human prostate cancer, and its effects are mediated through the suppression of tumor angiogenesis and activation of tumoricidal host effector cells as taught by Dong et al., one of ordinary skilled artisan would have been further motivated to utilize insects cells infected with a recombinant baculovirus expressing IFNβ, especially IFNβ has been taught to be more potent than IFN-α at least in inhibiting for the proliferation of human prostate cancer cells by Dong et al.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on June 02, 2003 in Paper No. 12 (pages 7-9) have been fully considered, but they are not found persuasive.

(1) Applicants argue that the failure of Examiner to comment on the likelihood of success, coupled with the Examiner's acknowledgement of the unpredictability of the physiological art, the rejection is therefore is fatally flawed.

Applicants' arguments are found unpersuasive because given the teachings provided by Sobol et al., Smith et al. (U.S. 6,224,882), Smith et al. (4,745,051; IDS) and Dong et al., coupled with a high level of skills of an ordinary skilled artisan at the

effective filing date of the present application, one of ordinary skilled artisan would have a reasonable expectation of success to practice the presently claimed invention. Furthermore, Sobol et al. have successfully demonstrated a method for inhibiting the growth of tumor cells in a patient comprising the stimulation of that patient's immune response against the tumor cells by administering to said patient a composition comprising tumor antigens (including in the form of inactivated viable tumor cells) and cytokine expressing cells genetically modified to express a variety of cytokine gene products, wherein said cytokine-expressing cells are not tumor cells (see Summary of the Invention, cols. 2-3; and the claims); Smith et al. have also successfully demonstrated that insect cells infected with recombinant baculovirus and expressing any selected desired gene products (including the human IFNβ gene product), and being utilized as an adjuvant for immunogenic, immunological, antigenic or vaccine compositions; and Dong et al. have shown that IFNβ is efficacious against many hematopoietic neoplasms, some vascular tumors as well as human prostate cancer. Then which specific aspects of the combined teachings are unpredictable?

(2) Applicants argue that the Sobol reference fails to mention IFN-β, while listing numerous other molecules and therefore it runs counter to scientific principles to simply substitute the teachings of Sobol using IL-2 with IFN-β. Applicants further argue that Sobol deal with the use of viable cells that express cytokines upon reintroduction into the host, and therefore the Sobol patent fails to evince to any degree that the mere administration of IFN-β in conjuction with insect cells would be a useful endeavor. Applicants argue further that there is no motivation to combine Sobol with Dong, which

teaches the use of transformed prostate cancer cells expressing IFN-β with aspects of Sobol that include non-viable host cells. Finally, applicants further argue that the Smith patents are not combinable with Sobol and Dong for the simple reason that advjuvants and live cellular cancer vaccines would not be used together because Sobol and Dong fail to mention the words "adjuvant" or "insect cells" and neither the Smith patents mentions transformed non-insect cells.

In response to applicant's arguments, it should be noted that this is a 103 rejection, therefore each cited references does not have to teach every element of the claims. Examiner would like to recite a paragraph from *in re Oetiker,* 977, F.2d 1443, 1448 (Fed. Cir. 1992).

> "[T]here must be some teaching, reason, suggestion, or motivation found "in the prior art" or "in the prior art references" to make a combination to render an invention obvious within the meaning of 35 U.S.C. 103 (1998). Similar language appear in a number of opinions and if taken literally would mean that an invention cannot be held to have been obvious unless something specific in a prior art reference would lead an inventor to combine the teachings therein with another piece of prior art. This restrictive understanding of the concept of obviousness is clearly wrong.... While there must be some teaching, reason, suggestion, or motivation to combine existing elements to produce the claimed device, it is not necessary that the cited references or prior art specifically suggest making the combination.... In sum, it is off the mark for litigants to argue, as many do, that an invention cannot be held to have been obvious unless a suggestion to combine the prior art teachings is found in a specific reference."

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re*

Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skilled artisan would have been motivated to carry out the above modification because insects cells genetically modified with a recombinant baculovirus expressing IFN-β not only serve as cytokine expressing cells but also function as an adjuvant for the co-administered inactivated tumor cells to further stimulate a systemic active immune response specific to said tumor cells in a patient. Additionally, IFNβ has been shown to be efficacious against many hematopoietic neoplasms, some vascular tumors as well as human prostate cancer, particularly IFNβ has been taught to be more potent than IFN-α at least in inhibiting for the proliferation of human prostate cancer cells as taught by Dong et al.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusions

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

GERRY LEFFERS
PRIMARY EXAMINER